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EXAMINER

MYERS, C

PAPER NUMBER **ART UNIT**

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No. 08/465,322

App

Soderlund

Examiner

Carla Myers

Group Art Unit 1655



X Responsive to communication(s) filed on Nov 29, 1999			
☐ This action is FINAL .			
☐ Since this application is in condition for allowance except for formal matters, in accordance with the practice under Ex parte Quay/1935 C.D. 11; 453 O.G. 213.			
A shortened statutory period for response to this action is set to expire3month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).			
Disposition of Claim			
Of the above, claim(s) is/are withdrawn from consideration			
Claim(s) is/are allowed.			
Claim(s) 51-69 is/are rejected.			
Claim(s) is/are objected to.			
☐ Claims are subject to restriction or election requirement.			
Application Papers See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.			
☐ The drawing(s) filed on is/are objected to by the Examiner.			
☐ The proposed drawing correction, filed on is ☐ approved ☐ disapproved.			
☐ The specification is objected to by the Examiner.			
☐ The oath or declaration is objected to by the Examiner.			
Priority under 35 U.S.C. § 119 Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d). All Some* None of the CERTIFIED copies of the priority documents have been received.			
☐ received. ☐ received in Application No. (Series Code/Serial Number)			
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).			
*Certified copies not received:			
☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).			
Attachment(s) Notice of References Cited, PTO-892 Information Disclosure Statement(s), PTO-1449, Paper No(s). Interview Summary, PTO-413 Notice of Draftsperson's Patent Drawing Review, PTO-948 Notice of Informal Patent Application, PTO-152			
— SEE OFFICE ACTION ON THE FOLLOWING PAGES			

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1. Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's second submission after final filed on November 29, 1999 has been entered.

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2. Claims 51-68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

With respect to claim 68, the specification does provide support for the embodiment of kits which comprise a target nucleic acid and a double stranded hybrid. Firstly, the specification does not describe any methods in which a double-stranded hybrid is formed. While the method described in the specification results in the formation of products which have a double-stranded region and a single-stranded region, the specification does not specifically teach primers which hybridize to the all but one nucleotide of the target and when extended by polymerase form a fully double-stranded molecule. That is, the molecules formed during the disclosed method are not fully double-stranded hybrids because the molecules comprise a 5' and 3' sequences which are single-stranded. Secondly, there is no suggestion or teaching in the specification to include the final reaction product of the double-stranded hybrid in the kit. With respect to claims 51-68, there is also no basis in the specification for a kit comprising the target nucleic acid to be detected. The specification at page 20 discusses kits comprising detection primers, nucleoside triphosphates and affinity labeled primers. The specification does not teach that target nucleic aids

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should be included in the kit. Also, there is no teachings in the specification of using target nucleic acids as controls and including control target nucleic acids in a kit. The methods disclosed in the specification require isolating the target nucleic acid from a biological source. Therefore, there is no basis in the specification for the concept of including in the kit a nucleic acid which is to be detected in the assay for detecting the presence of a specific nucleotide.

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In the response filed November 29, 1999, Applicants traversed this rejection by stating that the specification provides support for double-stranded hybrids. Applicants point to figure 1 as demonstrating a double-stranded hybrid. However, the teachings in the specification of the formation of the reaction product of the target nucleic acid and the primer indicate that the final reaction product comprises a region that is double-stranded and flanking 5' and 3' regions which are single-stranded. In all examples discussed in the specification, the primer is hybridized to a naturally occurring target nucleic acid. The specification does not discuss or exemplify methods in which the primer is hybridized to a synthesized nucleic acid which consists of only the sequence complementary to the primer and an adjacent 3' nucleotide. Accordingly, the specification does not provide support for fully double-stranded hybrids. Secondly, the specification does not provide support for including the target nucleic acid and the double-stranded nucleic acid reaction product in a kit. The specification at page 20 discusses kits comprising detection primers, nucleoside triphosphates and affinity labeled primers. The specification does not contemplate kits comprising the final reaction product, i.e. double-stranded hybrids or kits comprising the target nucleic acid.

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3. Claims 54-62, 68 and 69 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 54-62 are indefinite over the recitation of "kit according to claim 51 having the sequence" because it is unclear as to what is meant by a kit having a sequence. The claims should be amended to clarify whether it is the detection primer or the target nucleic acid which comprises the recited sequences.

Claim 68 is indefinite over the recitation of "double stranded hybrid" because it is unclear as to what constitutes such a hybrid. For example, it is unclear as to whether this refers to a nucleic acid molecule that contains a double-stranded region and a single-stranded region or if this refers to a fully double-stranded molecule consisting of a target nucleic acid and a primer that has been extended by one nucleotide

Claim 69 is indefinite and confusing because it is not clear as to what constitutes "the sequence" in the phrase "wherein the sequence between the 3' end of the oligonucleotide detection primer and the specific nucleotide at the predetermined position in the target nucleic acid". Does this refer to the sequence on the strand that is being extended or the sequence of the target nucleic acid? In the later case, it is unclear as to how this sequence does not contain the same specific nucleotide as the predetermined position since the only sequence present between the primer and the predetermined sequence is the same nucleotide at the predetermined position. In the former case, it is unclear as to how this recitation further limits the claim or applies to the claim because the nucleotide immediately 3' to the primer would be complementary to the

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nucleotide at the predetermined position and therefore couldn't possibly "contain a nucleotide residue of the same type as the specific nucleotide at the predetermined position". The claim as written implies that there are multiple nucleotides present between the 3' end of the primer and the predetermined position. However, the claim also indicates that no residues are present between the position complementary to the 3' end of the primer and the predetermined position since the primer flanks the 3' end of a predetermined position. In one aspect, the claim refers to a primer which flanks a predetermined position. Yet, the claim also refers to a primer that is extended to incorporate a nucleotide complementary to the predetermined position. Therefore, it is unclear as to what constitutes the oligonucleotide primer extension product. Clarification of the claim is required.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claim 69 is rejected under 35 U.S.C. 102(e) as being anticipated by Erlich.

Erlich (see, for example, col. 8) teaches primers useful for the amplification of target nucleic acids containing a variable nucleotide, such as a polymorphism/mutation. In particular, Erlich teaches the primer "DB01" (see columns 29 and 30), which hybridizes to the target nucleic acid so that the 3' nucleotide of the primer is immediately adjacent to a variable nucleotide and extension of the primer results in the addition of a nucleotide complementary to a first or second

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nucleotide residue. It is pointed out that the 3' residue of the DB01 primer flanks the "CTT" codon, which is present as a "GTG" codon in allelic variants and thereby the "C" nucleotide adjacent to the primer is considered to be a variable or mutated nucleotide and the "C" and "G" nucleotides are considered to be a first and a second "nucleic acid residue at a defined site". Hybridization of the primer to the target nucleic acid results in a primer extension product comprising an oligonucleotide primer hybridized to a target nucleic acid wherein the primer may be extended by a polymerase to add a nucleotide complementary to a predetermined position in the target nucleic acid.

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In the response of Paper No. 24, Applicants traverse this rejection by stating that Erlich does not teach a primer extension product comprising a labeled nucleotide complementary to a specific nucleotide at a predetermined position. This argument is not persuasive because the claim as written does not clearly include a limitation that the primer extension product has a labeled 3' nucleotide residue. As discussed above in the rejection under 35 U.S.C. 112, second paragraph, the recitation in claim 69 of the "primer has been extended by an enzyme catalyzed extension nucleic acid polymerization" is unclear because the claim previously refers only to a primer extension product having a primer that hybridizes to a target nucleic acid flanking the 3' predetermined region. The claim is drawn to a product, not a method of making the product, and it is unclear as to how the recitation of extending the primer relates to the product itself. If Applicants intend to claim a primer extension product comprising a 3' labeled nucleotide complementary to a specific nucleotide at a predetermined position, then the claims should be amended to include this specific recitation.

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5. Claim 69 is rejected under 35 U.S.C. 102(e) as being anticipated by Bajaj (U.S. Patent No. 5,846,710).

Bajaj teaches methods for screening for a variation in the sequence of a target nucleic acid at a predetermined position wherein the method comprises hybridizing a primer consisting of a sequence that hybridizes to a region immediately flanking the predetermined position, extending the primer using a DNA polymerase to incorporate a labeled nucleotide, and detecting the presence of a labeled primer extension product so as to determine the sequence at the predetermined position. The method of Bajaj results in the formation of a primer extension product comprising a oligonucleotide primer having a sequence complementary to a target nucleic acid and having a 3' labeled nucleotide complementary to a predetermined position in the target nucleic acid.

- 6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:
 - (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

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Claims 51-53, 63-69 are rejected under 35 U.S.C. § 103 as being unpatentable over Erlich (U.S. Patent No. 5,310,893) in view of Mullis (U.S. Patent No. 4,683,202; cited in the IDS of Paper No. 5).

Erlich (see, for example, col. 8) teaches primers useful for the amplification of target nucleic acids containing a variable nucleotide, such as a polymorphism/mutation. In particular, Erlich teaches primer "DB01" (see columns 29 and 30), which hybridizes to the target nucleic acid so that the 3' nucleotide of the primer is immediately adjacent to a variable nucleotide and extension of the primer results in the addition of a nucleotide complementary to a first or second nucleotide residue. It is pointed out that the 3' residue of the DB01 primer flanks the "CTT" codon, which is present as a "GTG" codon in allelic variants and thereby the "C" nucleotide adjacent to the primer is considered to be a variable or mutated nucleotide and the "C" and "G" nucleotides are considered to be a first and a second "nucleic acid residue at a defined site". Erlich teaches that primers may be 15 to 25 nucleotides in length (col. 4) and teaches that the DB01 primer is 21 nucleotides in length (col. 29). Erlich also teaches that, following the amplification reaction, the sequence of sample nucleic acids can be determined and confirmed by dideoxy chain termination sequencing. It is conventional in the field of dideoxy chain termination sequencing to use labeled dideoxyribonucleotide triphosphates to facilitate detection of the sequencing products. Erlich further teaches that the amplification reaction is performed using dNTPS and a polymerase. It is stated that the amplification may be performed using labeled reagents in order to allow for the detection of the amplification products and Erlich exemplifies methods in which the primers are labeled with detectable moieties (see, for example, col. 5). Erlich does not exemplify methods

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using labeled dNTPS. However, Mullis (col. 14) teaches that in PCR either the primer or the dNTPS may contain detectable moieties. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Erlich so as to have amplified the target nucleic acids using labeled dNTPs in place of labeled primers in order to have provided an equally effective means for facilitating detection of the amplification products. Such a modification of the method of Erlich would have resulted in a method which comprised the use of the reagents of a target nucleic acid, a DB01 oligonucleotide primer consisting of a sequence that hybridizes to the target nucleic acid immediately adjacent to a variable nucleotide position, labeled nucleotides and/or labeled dideoxynucleotide triphosphates, and a polymerase. Erlich does not specifically disclose a kit comprising each of these reagents. However, Erlich (col 26) does suggest that kits should be prepared containing all of the reagents required to practice the disclosed amplification technique wherein such kits comprise, for example, a primer, the substrate nucleoside triphosphates, means used to label, and an agent used to catalyze primer extension. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated a kit for practicing the method of Erlich which contained the reagents of target nucleic acid, the DB01 amplification primer, labeled nucleotides or labeled dideoxynucleotides and a polymerase in order to have achieved the expected benefits of convenience and cost-effectiveness for practioners of the art. With respect to claims 63 and 67, Erlich does not specifically exemplify a DB01 primer having attached thereto an "attachment moiety" through which the primer can be immobilized or immobilization of the primer and the amplification product onto a solid support. However, Erlich does teach that primers

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useful for amplifying variable nucleotides can be modified so as to attach labels thereto, including labels which can be used to capture the primer and facilitate immobilization of the primer onto a solid support (see col. 5). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the amplification primer of Erlich so as to have attached an affinity moiety to the primer to allow for the immobilization of the primer in order to have accomplished the expected advantage of generating a primer which could easily be immobilized onto a solid support to have allowed for the rapid and efficient separation and isolation of the nucleic acids comprising the amplification primer from other nucleic acids.

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In the response of Paper No. 24, Applicants traversed the previous grounds of rejection by stating that the cited references do not teach the inclusion of a specific labeled nucleotide complementary to the predetermined position of the target nucleic acid. Applicants arguments amount to a separate critique of the 2 cited references. Such arguments are entitled to little weight, where, as here, the rejection is based upon the combined disclosure of the references. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). The references when taken together teach the inclusion of labeled dNTPs which comprise a specific labeled nucleotide complementary to the nucleotide immediately adjacent to the 3' end of the DB01 primer and thereby complementary to the variable/"predetermined" position of the target nucleic acid.

7. Claims 51, 53, 64, 68 are rejected under 35 U.S.C. § 103 as being unpatentable over Bajaj (U.S. Patent NO. 5,846,710).

Bajaj teaches methods for screening for a variation in the sequence of a target nucleic acid at a predetermined position wherein the method comprises hybridizing a primer consisting of a

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sequence that hybridizes to a region immediately flanking the predetermined position, extending the primer using a DNA polymerase to incorporate a labeled nucleotide, and detecting the presence of a labeled primer extension product so as to determine the sequence at the predetermined position. The method of Bajaj requires the use of a DNA polymerase, a labeled nucleotide complementary to the nucleotide at the predetermined position and a detection primer. Bajaj does not teach packaging the reagents required to perform the detection assay in a kit. However, reagent kits for performing diagnostic methods were conventional in the field of molecular biology at the time the invention was made. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the detection primer, labeled nucleotide and DNA polymerase in a kit for the expected benefits of convenience and cost-effectiveness for practioners in the art wishing to determine the nucleotide sequence of a target nucleic acid at a predetermined position. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have included a control target nucleic acid in the kit in order to have provided a means for ensuring the accuracy of the detection method.

8. Claims 52, 63, and 65-67 are rejected under 35 U.S.C. § 103 as being unpatentable over Bajaj in view of Erlich.

The teachings of Bajaj are presented above. Bajaj does not teach labeling the detection primer with an affinity moiety that allows for immobilization of the primer onto a solid support.

Erlich teaches methods of nucleic acid amplification. Erlich teach that primers useful for amplifying variable nucleotides can be modified so as to attach labels thereto, including labels

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which can be used to capture the primer and facilitate immobilization of the primer onto a solid support (see col. 5).

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In view of the teachings of Erlich, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the primer of Bajaj so as to have attached an affinity moiety to the primer to allow for the immobilization of the primer, and to have included the affinity labeled primer in a kit, in order to have accomplished the expected advantage of generating a primer which could easily be immobilized onto a solid support to have allowed for the rapid and efficient separation and isolation of the nucleic acids comprising the amplification primer from other nucleic acids.

With respect to claims 65 and 66, Bajaj does not teach kits comprising a labeled dideoxynucleotide triphosphate. However, Erlich teaches methods for detecting nucleotide variation at a predetermined position in a target nucleic acid. The method of Erlich utilizes allele specific probes which specifically hybridize to a region of the target nucleic acid containing the predetermined nucleotide position. Erlich also teaches that following methods employing allele specific probes, the sequence of sample nucleic acids can be determined and confirmed by dideoxy chain termination sequencing. It is conventional in the field of dideoxy chain termination sequencing to use labeled dideoxyribonucleotide triphosphates to facilitate detection of the sequencing products. In view of the teachings of Erlich, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have further modified the method of Bajaj so as to have sequenced the target nucleic acid following the detection method in order to have confirmed the presence of a mutation in the target nucleic acid so as to have provided a

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more accurate assay for detecting nucleotide variation in a target nucleic acid. It would have been further obvious to one of ordinary skill in the art at the time the invention was made to have packaged the labeled dideoxynucleotide triphosphates in the kit comprising reagents for performing the detection method of Bajaj in order to have provided a kit which allowed one to confirm the presence of a mutation in a target nucleic acid using conventional dideoxy sequencing techniques.

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9. Claims 54-57 are rejected under 35 U.S.C. § 103 as being unpatentable over Bajaj in view of Emi (Genomics (1988) 3:373-379).

The teachings of Bajaj are presented above. Bajaj teaches that the detection primer comprises sequences complementary to the target nucleic acid and that the detection primer terminates immediately 3' to the predetermined nucleotide position. The primers must be sufficiently long to prime the synthesis of an amplification product and preferably are of a length of about 18 nucleotides. It is stated that the detection method can be used to detect nucleotide variation in any target gene, including the beta-globin gene and ras oncogene (col. 5). However, Bajaj does not specifically teach primers for detecting mutations in the ApoE gene. Emi teaches allele specific probes for detecting mutations in the apoE gene was known. In view of the teachings of Bajaj of how to select primers for detecting nucleotide variation and in view of the teachings of Emi of the specific mutations in the apoE gene and the disclosure of allele specific probes for detecting these mutations, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated primers of about 18 nucleotides comprising

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sequences complementary to the apoE gene immediately flanking the modified nucleotide encoding codons 112 and 158 and thereby to have generated comprising sequences identical to those of the instantly claimed primers in order to have provided primers and kits comprising said primers useful for the detection of sequence variation in the apoE gene.

10. Claims 58-59 are rejected under 35 U.S.C. § 103 as being unpatentable over Bajaj in view of Saiki (Nature (1986) 324:163-166).

The teachings of Bajaj are presented above. Bajaj teaches that the detection primer comprises sequences complementary to the target nucleic acid and that the detection primer terminates immediately 3' to the predetermined nucleotide position. The primers must be sufficiently long to prime the synthesis of an amplification product and preferably are of a length of about 18 nucleotides. It is stated that the detection method can be used to detect nucleotide variation in any target gene, including the beta-globin gene and ras oncogene (col. 5). However, Bajaj does not exemplify primers for detecting mutations in the beta-globin gene. Saiki teaches allele specific probes for detecting mutations (A to T) in codon 6 of the beta-globin gene. Furthermore, at the time the invention was made the complete sequence of the beta-globin gene was known. In view of the teachings of Bajaj of how to select primers for detecting nucleotide variation and the suggestion of Bajaj to generate primers for detecting nucleotide variation in the beta-globin gene and in view of the teachings of Saiki of the specific mutation in the beta globin gene leading to sickle cell anemia and the disclosure of allele specific probes for detecting this mutation, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated primers of about 18 nucleotides comprising sequences

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complementary to the beta-globin gene immediately flanking the modified nucleotide encoding codon 6 and thereby to have generated comprising sequences identical to those of the instantly claimed primers in order to have provided primers and kits comprising said primers useful for the detection of the sickle cell mutation.

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11. Claims 60-62 are rejected under 35 U.S.C. § 103 as being unpatentable over Bajaj in view of Farr et al (PNAS (1988) 85:1629-1633; cited on IDS of Paper No. 5).

The teachings of Bajaj are presented above. Bajaj teaches that the detection primer comprises sequences complementary to the target nucleic acid and that the detection primer terminates immediately 3' to the predetermined nucleotide position. The primers must be sufficiently long to prime the synthesis of an amplification product and preferably are of a length of about 18 nucleotides. It is stated that the detection method can be used to detect nucleotide variation in any target gene, including the beta-globin gene and ras oncogene at codon 12 (col. 5). However, Bajaj does not exemplify primers for detecting mutations in the ras oncogene. Farr teaches allele specific probes for detecting mutations in codon 12 of the ras oncogene (see Table 1). Furthermore, at the time the invention was made the complete sequence of the ras oncogene was known. In view of the teachings of Bajaj of how to select primers for detecting nucleotide variation and the suggestion of Bajaj to generate primers for detecting nucleotide variation in the ras oncogene and in view of the teachings of Farr of the specific mutations in the ras oncogene and the disclosure of allele specific probes for detecting these mutations, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated primers of about 18 nucleotides comprising sequences complementary to the ras oncogene

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immediately flanking the modified nucleotide encoding codon 12 and thereby to have generated comprising sequences identical to those of the instantly claimed primers in order to have provided primers and kits comprising said primers useful for the detection of genetic variation in the ras oncogene.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-305-3014 or (703)-305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

April 26, 2000

CARLA J. MYERS PRIMARY EXAMINER